REMARKS

Claim Amendments

Claims 1 and 17 have been amended to refer to all the six CDR regions, support for this amendment is found one page 8 lines 24-34:

> The present invention also relates to anti-idiotypic antibodies wherein the complementarity determining regions (CDR) of the variable heavy and/or light chains of said antibody have at least 70 % sequence identity, more preferably have at least 80 % sequence identity, even more preferably have at least 90 % sequence identity, and most preferably have at least 95-99 % sequence identity with the corresponding amino acid sequences depicted in SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9 and SEQ ID NO 10 or are identical to the corresponding amino acid sequences depicted in SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9 and SEQ ID NO 10, thereby preferably retaining the ability to neutralise inhibitory FVIII antibodies.

Claims 1 and 17 have furthermore been amended to recite "capable of neutrali[z]ing a human Factor VIII inhibitory antibody." Support for this language is found, for example, on page 15, lines 22-23, which states: "The present invention relates to anti-idiotypic antibodies capable of neutralising the inhibitory effect of FVIII inhibitors."

Claims 1 and 17 have also been amended in that the phrase "said antibody" is replaced by the phrase "said anti-idiotypic antibdy."

Claim 17 has been amended to refer to an anti-idiotypic antibodies comprising all of the complementarity determining regions (CDR) of the variable heavy or light chains of the anti-idiotypic antibodies have at least 95% sequence identity to the corresponding amino

acid sequences recited. Support for this amendment is found, for example, at page 8 lines 24-34.

Claim 20 has been amended to refer to a modified version of an antibody fragment. Support for these amendments is found on page 9 line 5-6 which states: "The invention also relates to modified versions of said fragments."

Claim 22 has been amended to refer to the Ab14C12 antibody produced by the deposited 14C12 cell line. Support for this amendment is found in the specification, for example, on page 7, lines 24 - 29, which states: "The cell line 14C12 was deposited [...] with Accession Number LMBP 5878CB."

Claim 22 has also been amended to recite antibody fragments. Support for this amendment is found, for example, on page 9, line 32 through page 10, line 8, and on page 18, lines 15-17, where it is stated: "A particular embodiment of the present invention is provided by the anti-idiotypic monoclonal antibody 14C12 and antibodies including antibody fragments derived therefrom."

New claims 32-36 have been added.

New claim 32 is directed to antibodies which are characterized in that they neutralize the anti-coagulant activity of FVIII inhibitors by at least 50% and in that they do not interact with the binding of FVIII to vWF and phopholipids. Support for this claim is found in the specification, for example, on page 16, lines 15 to 20:

> According to a particular embodiment the present invention relates to ant[i]-idiotypic antibodies against human Factor VIII inhibitory antibodies directed

against the C2 domain of FVIII capable of neutralising by at least 50% the inhibition of FVIII procoagulant activity of inhibitory antibodies directed against the C2 domain of FVIII, but which do not inhibit interfere with the physiological activity of FVIII, more particularly the binding of FVIII to vWF or PL.

New claim 33 relates to antigen binding fragments of the antibodies of claim 1. Support for this claim is found in the specification, for example , for example, on page 9, line 32 through page 10, line 8, and on from page 18, line 26 to page 19, line 5:

> The present invention also provides fragments and modified versions of the anti-idiotypic antibody of the present invention, in particular fragments comprising complementarity determining regions ("CDR's") of the monoclonal anti-iditioypic antibodies, obtained as described above, as well as modified versions thereof. For instance, the invention provides antigen-binding fragments Fab, Fab' and F (ab')2 generated by proteolytic digestion of the said monoclonal antibodies using methods well known in the art, such as described by Stanworth et al., Handbook of Experimental Immunology (1978), vol. 1 chapter 8 (Blackwell Scientific Publications). Such fragments or artificial sequences, which contain the antibody binding site, may or may not have lost a number of properties of the parent antibody, such as complement activation or capacity to bind to Fc gamma receptors, however without losing their ability to inhibit inhibitory antibodies against FVIII.

New claims 34 to 36 are directed to pharmaceutical compositions which include the anti-idiotypic antibodies and fragments thereof as recited in claims 17, 20, or 33, respectively. This claim is supported at least by claim 14 of the application as filed (PCT/EP2003/008365) and the section of the specification on page 20, lines 25 to 30.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 17, 20, and 22 stand rejected under 35 U.S.C. § 112, second paragraph on various grounds. Each of these rejections should be be withdrawn in view of the present amendments.

Rejections under 35 U.S.C. §112, first paragraph

Enablement

The Examiner alleges that applicant's specification does not appear to provide guidance for the antibodies of claims 1, 17-22, 24, and 26. Applicants submit that the present claim amendments address the issues raised in the Office action. The present amendments, for the record, were made to expedite prosecution, and applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application

The Examiner has also indicated that the specification does not provide guidance for antibodies derived from 14C12 as recited in claim 22. Claim 22, as amended, refers to antibody fragments derived from Ab14C12 produced by the 14C12 cell line wherein said antibody fragment is capable of neutralizing said inhibitory antibody.

On this point, applicants submit that it was within the skill of the artisan to identify, at the time of filing, for a given anti-idiotypic antibody, the sequence of each of the CDR sequences of the given anti-idiotypic antibody. Furthermore, it was within the skill of the

artisan to identify antibodies having at least 70% sequence identity with the given antibody within the CDR regions which maintain the ability to neutralize an inhibitory antibody of FVIII. Indeed, the specification provides a method for determining the ability of antibodies to neutralize an anti-FVIII antibody. This method is illustrated in Example 2, page 26-28 of the specification.

Deposit

Claim 25 was also rejected as failing to comply with the enablement requirement. Applicants note that hybridoma LMBP 5878CB was deposited under the terms of the Budapest Treaty as identified on the receipt of the Belgian Coordinated Collections of Microorganisms (BCCM™), which was included in the application as filed on page 7, lines 25-29, which states:

> The cell line 14C12 was deposited on July 30, 2002 at the Belgian Coordinated Collections of Micro-organisms (BCCM), LMBP (plasmid collection, Laboratorium voor Moleculaire Biologie,Universiteit, K. L. Ledeganckstraat 35, 9000 Gent, Belgium) with Accession Number LMBP 5878CB.

This description clearly provides the accession number for the deposit, the date of the deposit, a description of the deposited biological material, and the name and address of the depository. Copies of Form PCT/RO/134 and supporting documentation as filed in connection with PCT/EP2003/008365 are transmitted herewith. These documents make clear that LMBP 5878CB was deposited under the terms of the Budapest Treaty. Nevertheless, to

advance prosecution, Applicants enclose a statement by Dr. Jean-Marie Saint-Rémy, with regard to the term of this deposit.

Written Description

Claims 1, 17-22, 24, and 26 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner considers that the recited structural features of the 14C12 antibody are not representative of the claimed genus because the important structural elements of 14C12 are not necessarily present in the claimed genus of antibodies.

To the extent the Examiner considers that this rejection still applies to the claims as presently amended, Applicants respectfully disagree. Claims 1 and 17, as amended, are directed to a genus of antibodies of which each of the CDR regions display at least 70% and 95% sequence identity with the recited CDR sequences, respectively. In addition, the genus requires the functional definition that the antbiodies are capable of neutralizing anti-idiotypic FVIII antibodies. Of this genus, antibody 14C12 is representative, as it contains the feature of having at least 70% sequence identity to the provided CDR sequences which is related to the functional limitation of neutralizing activity. Applicants submit that as such the structural feature of "70% sequence identity" (as well as 95% sequence identity) is an important structural element. Indeed, it is a feature that is can easily be determined by the person of skill in the art and that can be identified unambiguously at all times, once a reference sequence is provided. It is precisely the contribution of the present invention to have

identified an antibody and more particularly the combination of sequences of CDRs which ensure neutralizing activity of inhibitory anti-FVIII antibodies. Sequence modifications within the 70% sequence identity range easily recognized and determined or introduced by the skilled person, and its effect on the neutralizing activity of the antibody is determined using the methods described in the specification referred to above. It is therefore inappropriate to consider that the inventors were not in possession of the invention or that there would be no guidance to the skilled person to identify or develop the claimed genus of antibodies.

It is noted in this regard that Janeway et al. referred to by the Examiner in fact confirms the fact that modification of antibodies was a technique known to the skilled person at the time. Indeed, Janeway et al. states (last paragraph prior to Summary on page 3:11): "Genetic engineering by site-directed mutagenesis can tailor an antibody binding site to its complementary antigenic epitope; this process has its natural counterpart in the maturation to higher affinity by the process of somatic hypermutation as an antibody response progresses, which we discuss later (see Section 3-18)". Thus, based on the available technology a skilled artisan could with reasonable expectation of success introduce a modification so as to obtain either the same or improved binding affinity. Finally, it is noted that the Examiner points to Rudikoff et al. as a "negative example." At the same time, positive examples can also be identified, e.g. WO2007/111965 (copy enclosed) discloses monoclonal antibodies capable of neutralizing hepatitis C virus. Two different antibodies are described which share, at amino

acid level 78% and 85% sequence identity in their heavy and light chains, respectively (Table 4, page 39 of WO200/111965), while inhibitory activity is maintained. As indicated above, inhibitory activity can be screened. Thus, this confirms that the skilled person, would be able to introduce modifications into an antibody and identify antibodies which maintain inhibitory activity with reasonable expectation of success.

For all of the foregoing reasons, Applicants respectfully request that the rejections under 35 U.S.C. 35 U.S.C. §112, first paragraph be withdrawn.

Transmitted herewith is a Petition to extend the period for replying to the Office action for two (3) months, to and including March 4, 2008, along with payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 3/4/2008

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